PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

7

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 255/02, 257/04 A61K 31/41, C07F 7/02	A1	(11) International Publication Number: WO 93/17003 (43) International Publication Date: 2 September 1993 (02.09.93)

(21) International Application Number: PCT/US93/01785

(22) International Filing Date: 26 February 1993 (26.02.93)

(30) Priority data:
07/842,295 26 February 1992 (26.02.92) US
07/842,299 26 February 1992 (26.02.92) US

(60) Parent Applications or Grants
(63) Related by Continuation
US 07/842,295 (CIP)
Filed on 26 February 1992 (26.02.92)
US 07/842,299 (CIP)
Filed on 26 February 1992 (26.02.92)

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : DREYER, Geoffrey, Bainbridge [US/US]; 2 Marlin Drive, Malvern, PA 19355 (US).

(74) Agents: KINZIG, Charles, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: RETROVIRAL PROTEASE INHIBITORS

(57) Abstract

The present invention provides compounds, more particularly dipeptide analogs, which bind to retroviral proteases. These compounds are inhibitors of retroviral proteases and are useful for treating diseases related to infection by retroviruses.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

RETROVIRAL PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to retroviral protease inhibitor compounds, pharmaceutical compositions thereof, and a method of treating retroviral diseases therewith, including a method of treating disease states associated with human immunodeficiency virus (HIV-1, HIV-2).

BACKGROUND OF THE INVENTION

Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Also known as RNA-tumor viruses, their presence has been associated with a wide range of diseases in humans and animals. They are believed to be the causative agents in pathological states associated with infection by Rous sarcoma virus (RSV), murine leukemia virus (MLV), mouse mammary tumor virus (MMTV), feline leukemia virus (FeLV), bovine leukemia virus (BLV), Mason-Pfizer monkey virus (MPMV), simian sarcoma virus (SSV), simian acquired immunodeficiency syndrome (SAIDS), human T-

lymphotropic virus (HTLV-I, -II) and human immunodeficiency virus (HIV-1, HIV-2), which is the etiologic agent of AIDS (acquired immunodeficiency syndrome)and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no effective method for treating this type of infection has been developed.

Retroviral replication occurs only in host cells. Critical to this replication is the production of functional viral proteins. Protein synthesis is accomplished by translation of the appropriate open reading frames into polyprotein constructs, which are processed, at least in part, by a viral protease into the functional proteins. The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh *et al.*, *Virology*, 145, 280-92(1985), Crawford, *et al.*, *J. Virol.*, 53, 899-907(1985) and Debouk, *et al.*, *Proc. Natl. Acad. Sci. USA*, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

The use of isosteric replacements has been disclosed as a strategy for the development of protease inhibitors for HIV-1. European Patent Applications EP-A 337 714, EP-A 357 332, EP-A 346 847, EP-A 342 541, EP-A 352 000, EP-A 393 445 and EP-A 434 365 are representative, and are incorporated herein by reference. These references disclose dipeptide analogs of the natural polyprotein substrates of retroviral proteases. As discussed therein, these dipeptide analogs bind selectively and competitively to retroviral proteases; however, the protease is unable to cleave the carbon-carbon bond presented to it instead of the scissile amide bond of the natural substrate. Thus, such compounds are useful for inhibiting viral replication by inactivation of the protease. The incorporation of heterocyclic elements in the P3' and P4' substrate positions of compounds containing a dipeptide isostere has been disclosed by deSolms *et al.*, *J. Med. Chem.*,

34, 2852 (1991). However, these compounds can be less than desirable for obtaining optimal drug delivery in mammalian organisms, particularly in humans. Some of these compounds can also have a less than desirable serum half-life, and therefore duration of action, because they contain amide bonds in relatively high proportion, and thus are prone to metabolic degradation, hepatic clearance, or other elimination mechanisms.

There exists a need for novel compounds which inhibit retroviral protease activity, and a need for compounds which possess desirable pharmacokinetic properties, such as for good drug delivery, metabolic stability, good serum half-life, duration of action and potency. Such pharmaceutical uses provide therapies for retroviral diseases in mammals, especially in humans, which have been heretofore difficult to treat.

SUMMARY OF THE INVENTION

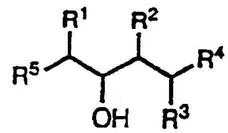
The present invention provides compounds, hereinafter represented as formula (I), which bind to retroviral proteases. These compounds are inhibitors of retroviral proteases and are useful for treating diseases related to infection by retroviruses.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention additionally provides a method for treating retroviral disease, comprising administering to a mammal in need thereof an effective amount of a compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are illustrated by formula (I):



(I)

wherein:

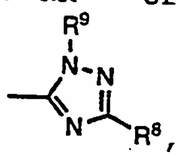
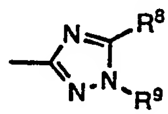
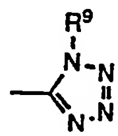
R^1 and R^3 are each independently Q, Q-C_{1-6}alkyl, Q-C_{2-6}alkenyl, Q-C_{2-6}alkynyl or C_{1-6}alkyl substituted by one to five fluorine atoms, each optionally substituted by R^{23};

Q is H, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, Ar or Het

R^2 is H or OH;

R^4 is R^6-NR^{11}- or $CONR^{11}CHR^6R^7$;

R^5 is R^6-NR^{11}- or R^{10}-NR^{11}-;

R^6 is ,  or ;

X is NR^{11}, O or S;

R^7 is Q, Q-C_{1-6}alkyl or Q-C_{2-6}alkenyl;

R^8 is H, OH, halo, NO_2, COR^{12}, CF_3, Ar, C_{1-6}alkyl-R^{15}, or $R^{17}(R^{18}R^{19}C)_m$;

R^9 and R^{11} are H or C_{1-4}alkyl;

R^{10} is A-$(B)_n$-;

R^{12} is R^7, OR^7, NR^7R^{11} or an amino acid or amino alcohol;

B is an amino acid;

A is H, Ar, Het, $R^{17}(R^{18}R^{19}C)_m$, Ar-W, Het-W or $R^{17}(R^{18}R^{19}C)_m$-W, or phthaloyl each optionally substituted by one to three groups chosen from R^{15} or C_{1-6}alkyl-R^{15};

W is C=O, OC(=O), NR^{11}C(=O), SC(=O), NR^{11}C(=S), SO_2, $NR^{11}SO_2$ or P(=O)(OR^{22});

R^{15} is H, nitro, C_{1-6}alkoxy, C_{1-6}alkylthio, O(C=O)R^{16}, C=OR^{22}, CO_2R^{22}, CON$(R^{16})_2$, N$(R^{22})_2$, NHC(=N)NH-A, I, Br, Cl, F, OR^{10}, or OH, provided that when R^{15} is a substituent of the carbon adjacent to W, R^{15} is not halogen or OH when W is OC(=O) or NHCO;

R^{16} is H or C_{1-6}alkyl;

R^{17}, R^{18} and R^{19} are independently: i) H, R^{15} or C_{1-4}alkyl, C_{2-6}alkenyl, phenyl, naphthyl, C_{3-6}cycloalkyl or Het, each optionally substituted by one to three R^{15} or

R^{15}-C_{1-6}alkyl groups, or ii) R^{17} is as above and ($R^{18}R^{19}C$) are joined together to form a phenyl, naphthyl, C_{3-6}cycloalkyl or Het ring, or iii) R^{17} is as above and R^{18} and R^{19} together are =O;

R^{22} is H, C_{1-6}alkyl, phenyl or phenyl-C_{1-4}alkyl;

R^{23} is $-X'-(CH_2)_qNR^{24}R^{25}$, $X''[((CH_2)_rO)_s]R^{26}$, $CH_2X''[((CH_2)_rO)_s]R^{26}$, or benzofuryl, indolyl, azacycloalkyl, azabicyclo C_{7-11}cycloalkyl or benzopiperidinyl, optionally substituted with C_{1-4}alkyl;

q is 2-5;

s is 1-6 and r is 1-3 within each repeating unit s;

X' is CH_2, O, S or NH;

X" is CH_2, NR', O, S, SO or SO_2;

R^{24} and R^{25} are i) C_{1-6}alkyl, optionally substituted by OH, C_{1-3}alkoxy, or $N(R')_2$, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, O, S, SO, SO_2, said heterocycle optionally substituted with C_{1-4}alkyl, iii) aromatic heterocycle, optionally substituted with C_{1-4}alkyl or $N(R')_2$;

R' is H or C_{1-4}alkyl;

R^{26} is H, C_{1-4}alkyl, $C(=O)R^{27}$, $C(=O)U[(CH_2)_mO]nR'$, $P(=O)(OM)_2$, CO_2R^{27}, $C(=O)NR^{27}R^{28}$, where M is a mono or divalent metal ion, and U is NR' or O;

R^{27} is C_{1-6}alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C_{1-3}alkoxy, $CONR'_2$, NR'_2, CO_2R', $SO_2NR'_2$, CH_2NR_2, NR'COR', $NR'SO_2R'$, $X''[(CH_2)_rO]_sR'$ or $CH_2X''[(CH_2)_rO]_sR'$;

R^{28} is H, C_{1-6}alkyl or together with R^{27} forms a 5-7 membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

m is 1-4; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be

any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*.

Formula (I) is intended to encompass all unique nonracemic stereoisomers which may occur due to the presence of asymmetric carbon atoms in the molecule. Such compounds may occur as pure enantiomers or diastereomers or as a mixture of individual stereoisomers. The definition of any substituent moiety which may occur more than once in formula (I) is independent of any other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Compounds of this invention which include acyclic double bonds may be present in either the cis (Z) or trans (E) geometrical configuration with respect to any two substituents. All tautomeric forms of the heterocycles, such as tetrazole and triazole are also within the scope of this invention.

Suitably R^1 and R^3 are C_{1-6}alkyl, Ar-C_{1-6}alkyl, Ar-C_{2-6}alkenyl, Ar-C_{2-6}alkynyl, C_{1-6}alkyl optionally substituted by one to five fluorine atoms or benzyl substituted in the 4-position by R^{23}. Preferably R^1 is benzyl and R^3 is phenylpropenyl or benzyl.

Suitably R^2 is H or OH. Preferably R^2 is H.

Preferably R^4 is $CONR^{11}CHR^6R^7$.

Suitably R^5 is R^{10}-NR^{11}. Preferably R^5 is C_{1-6}alkyloxycarbonyl, pyridinylmethyloxycarbonyl or aryloxycarbonyl. More preferably R5 is t-butyloxycarbonylamino or isopropyloxycarbonylamino.

Preferably R^6 is triazole.

Preferably R^7 is C_{1-6}alkyl. Isopropyl is most preferred.

Suitably R^8 is H, C_{1-6}alkyl, NH_2, NO_2 or COR^{12}. Preferably R^8 is H.

Preferably R^9 is H.

Suitably B is Ala or Val. Preferably m is 0 and B is absent.

Preferably W is OC(=O).

Suitably R^{23} is hydroxy-C_{1-4}alkoxy, C_{1-4}alkoxy-C_{1-4}alkoxy, or $-O(CH_2)_2NR^{24}R^{25}$, wherein R^{24} and R^{25} are are a 5- or 6-membered heterocycle, such as morpholino.

Representative compounds of this invention are:

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxy-carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(1-phenylpropyn-3-yl)-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(*trans*-1-phenylpropen-3-yl)-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(tetrazol-5-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-nitro-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-amino-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide; and

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(4,4,4-trifluorobutyl)-hexanamide.

A preferred compound is (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

The term "alkyl" as used herein refers to a straight or branched chain alkyl radical of the indicated number of carbon atoms. "C_{1-4}alkyl" as applied herein is meant to include methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

sec-butyl, *tert*-butyl; "C_{1-6}alkyl" includes additionally pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 2-ethylpropyl, neopentyl, *n*-hexyl 2,2-dimethylbutyl, 2-methylpentyl, and the like. "Alkoxy" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging oxygen atom. "Alkylthio" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging sulfur atom.

"Alkenyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms, which contains one or more carbon-carbon double bonds at any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, 2-methylpropenyl, hexenyl, and the like.

"Alkynyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms which contains a carbon-carbon triple bond at any stable point along the chain, such as ethynyl, 2-propynyl, 2-butynyl, 4-pentynyl, 2-methyl-3-propynyl, hexynyl and the like.

"Cycloalkyl" refers to a saturated ring group of the indicated number of carbon atoms. "C_{3-7}cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. "Cycloalkenyl" refers to a saturated ring group of the indicated number of carbon atoms, having at least one endocyclic carbon-carbon double bond. "C_{5-7}cycloalkenyl" includes cyclopentenyl, cyclohexenyl and cycloheptenyl.

"Aryl", abbreviated as Ar, refers to phenyl or naphthyl, optionally substituted with one to three halo, OH, OR^{10}, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, CF_3, amino, NO_2, carboxy, C_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-6}alkyl-Het, C_{1-6}alkoxy-Het, C_{1-6}alkyl-phenyl, C_{1-6}alkoxy-phenyl, C_{1-6}alkyl-, C_{1-6}alkoxy-, HetC_{1-6}alkyl-, HetC_{1-6}alkoxy-, phenylC_{1-6}alkyl-, phenylC_{1-6}alkoxy- or phenyloxy.

As used herein except where noted, the term "heterocycle", abbreviated as "Het", represents a stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N,

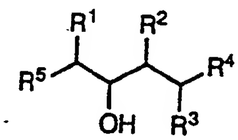
O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one to three halo, OH, alkyl, alkoxy, alkyl-Het, alkoxy-Het, alkyl-phenyl, alkoxy-phenyl.

"Amino acid" means the D- or L- isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine or trifluoroalanine. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). Usually lipophilic amino acids are preferred for the moiety B, for instance, Val, Ala, Leu and Ile. It will be understood that a linkage B-O refers to an oxygen atom bonded to the carboxyl group of an amino acid, and that a B-N linkage indicates a nitrogen atom bonded to the carboxyl group of an amino acid, as in an amide bond. "Amino alcohol" refers to an amino acid in which the carboxyl group has been reduced to a methylene hydroxy group.

Certain chemical names are abbreviated herein for the sake of convenience. Boc refers to the *t*-butoxycarbonyl radical. Cbz refers to the carbobenzyloxy radical. Bzl refers to the benyzl radical. Ac refers to acetyl. Ph refers to phenyl. BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. DCC refers to dicyclohexylcarbodiimide. DMAP refers to dimethylamin-opyridine. DMSO refers to dimethylsulfoxide. HOBT refers to 1-hydroxybenzotriazole. NMM is N-methylmorpholine. DTT is dithiothreitol. EDTA is ethylenediamine tetraacetic acid. DIEA is diisopropyl ethylamine. DBU is 1.8 diazobicyclo[5.4.0]undec-7-ene. DMSO is dimethylsulfoxide. DMF is dimethyl formamide; Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-

diphosphetane-2,4-disulfide and THF is tetrahydrofuran. HF refers to hydrofluoric acid and TFA refers to trifluoroacetic acid.

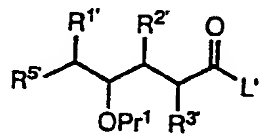
The compounds of formula (I):



(I)

wherein R^4 is CO-NR'CHR^{6}R^7, R^5 is $R^{10}R^{11}N$-, and R^1, R^2, R^3 and R^6 are as defined in formula (I), are prepared by:

1) (a) coupling a compound of the formula (II):



(II)

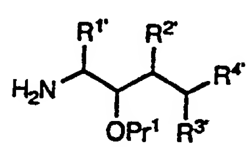
with a compound of formula (III):

$$HR'N\text{-}CHR^{6'}R^{7'}$$

(III)

where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{5'}$, $R^{6'}$ and $R^{7'}$ are R^1-R^7, respectively, as defined for formula (I) with any reactive groups protected, Pr^1 is H or a hydroxyl protecting group, and L' is OH or a leaving group; or

(b) coupling a compound of the formula (IV):



(IV)

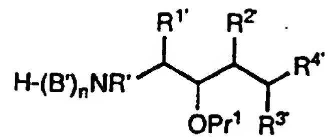
with a compound of the formula (V):

$$A'\text{-}(B')_n\text{-}L'$$

(V)

wherein A' and B' are as defined in formula (I) with any reactive groups protected; or

(c) coupling a compound of the formula (VI):



(VI)

with a compound of the formula (VII):

A'-L'

(VII)

and,

2) if appropriate, a coupling agent; and

3) removing any protecting groups and

4) forming a pharmaceutically acceptable salt thereof.

The coupling reactions may be accomplished by activating the substrate with a reactive functional group *in situ* or prior to the coupling reaction, such that it is reactive with an amino group. For instance, acids may be converted to acid chlorides, bromides, activated esters or anhydrides, or by adding a coupling reagent. Coupling agents are well known in the art for activating a functional group *in situ*. Exemplary of such agents are DCC and other carbodiimides, DMAPEC, BOP and PPA. These coupling agents may optionally be used with other reagents, such a HOBT, NMM and DMAP, which may facilitate the reaction.

Suitable leaving groups, L', are those which are displaceable by an amino group, such as bromo, chloro, a substituted acyl (eg. trifluoroacetyl, bromobenzoyl, nitrobenzoyl) or a substituted phenol (eg. 4-nitrophenol) and the like. If L' is OH, so that A-OH is an acid, it will be appropriate to use a coupling agent as hereinbefore described.

For instance:

When A is a substituted alkyl group, such as $R^{17}(R^{18}R^{19}C)_m$, L' may be a bromo, chloro, iodo or an alkyl or aryl sulonate.

When A is $R^{17}(R^{18}R^{19}C)_m$-W, Ar-W or Het-W, and W is C=O, A-L' may be a carboxylic acid halide, activated ester or anhydride, or a carboxylic acid in the presence of a coupling agent. Methods for preparing such compounds are well known.

When W is OC=O, A-L' may be a chloro- or bromo-formate, or an activated carbonate. Haloformates may be prepared by reacting the appropriate alcohol with phosgene or carbonyldibromide. Activated carbonates may be prepared by reacting the appropriate alcohol with a suitable carbonate such as bis(4-nitrophenyl)carbonate.

When W is SO_2, A-L' may be a sulfonyl halide which may be prepared from the corresponding sulfonic acid.

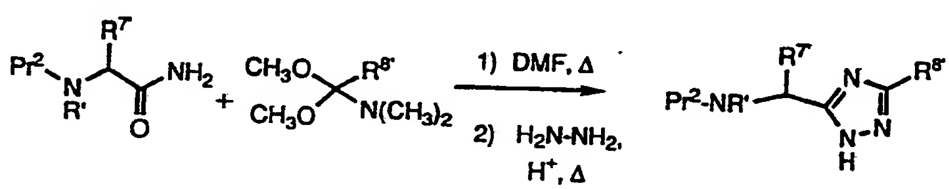
When W is SC=O, A-L' may be a halothioformate, which may be prepared from a carbonyldihalide and an appropriate mercaptan.

When W is $PO(OR^{22})$, A-L' may be a phosphonyl halide, which may be prepared from the corresponding phosphonic acid.

Compounds wherein A is $R^{17}(R^{18}R^{19}C)_m$-W, Ar-W or Het-W, and W is NR'C=O are ureas, and may be prepared by reacting a compound of formula (VII) with an isocyanate of the formula $R^{17}(R^{18}R^{19}C)_m$-NCO, Ar-NCO or Het-NCO, in a suitable solvent such as methylene chloride, optionally with heating.

Compounds of formula (III), wherein R^6 is a triazole are prepared according to routine method, such as illustrated in Scheme 1, wherein Pr^2 is a removeable amino protecting group, and $R^{7'}$ and $R^{8'}$ correspond to R^7 and R^8 as defined for formula (I), or a group which may be converted into R^7 or R^8, with any reactive groups protected.

Scheme 1



The amino carboxamides are generally known or are prepared by methods well known in the art, for instance, by treating a suitably protected α-amino acid ester with ammonia. Reaction of the an α-amino carboxamide with a suitable carboxamide acetal or ketal yields an acyl amidino intermediate which may be further reacted *in situ* with hydrazine, or a substituted

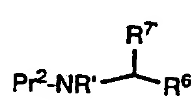
hydrazine, in the presence of an acid to yield the desired triazole. For instance, N-benzyloxycarbonyl-alaninamide may be heated with dimethylformamide dimethylacetal to yield N-[(N-benzyloxycarbonyl)alanyl]-formamidine; and further reacted with hydrazine and acetic acid to yield 1-benzyloxycarbonylamino-1-(1,3,4-trazol-2-yl)ethane. Further modification of the triazole by alkylation, if desired, may be accomplished by routine methods. For instance, the triazole may be treated with an alkyl halide. Subsequent removal of the amino protecting group yields a compound of formula (III).

Compounds of formula (III), wherein R^6 is a tetrazole are prepared from a suitably protected α-amino nitrile with azide as illustrated in Scheme 2. For instance, 2-

Scheme 2

(benzyloxycarbonyl) amino-butyronitrile may be heated with ammonium chloride and sodium azide in anhydrous dimethylformamide to yield the corresponding 1-(benzyloxycarbonyl)amino-1-(tetrazol-5-yl)propane. Subsequent removal of the protecting group, *e.g.*, the benzyloxycarbonyl group may be removed by hydrogenation over a palladium catalyst, yields a tetrazole compound of formula (III). Suitable α-amino nitriles may be prepared by routine procedures from α-amino carboxamides, such as by dehydration of the carboxamide with phosphorous pentachloride.

Intermediate compounds of formula (VIII):

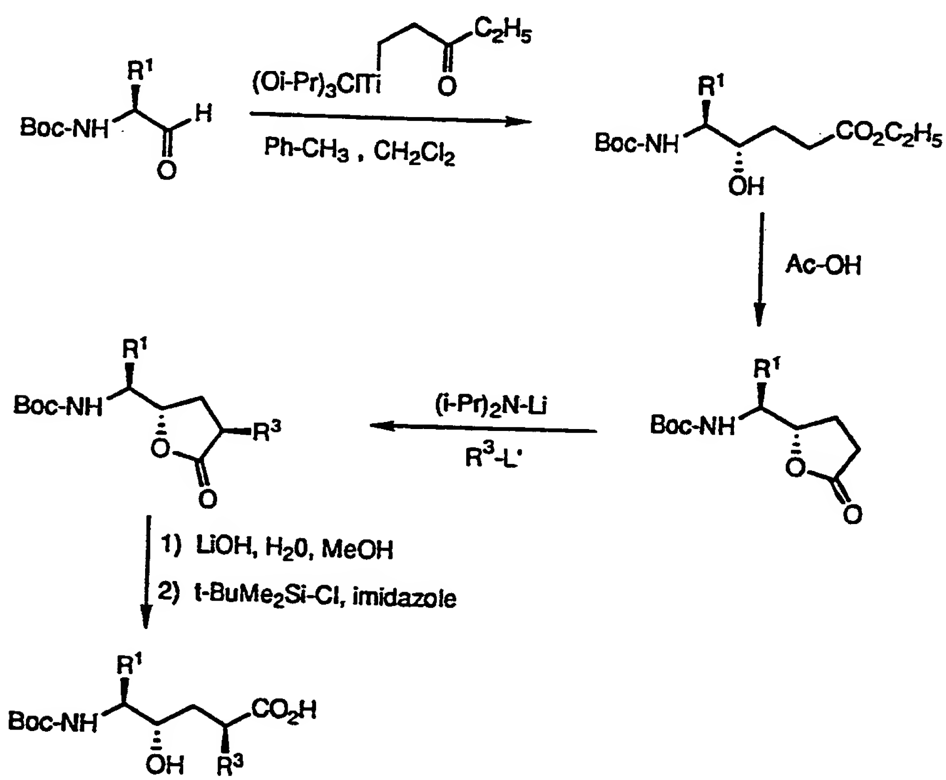


(VIII)

wherein Pr^2 is an amino protecting group, R^6 is as defined for formula (I) and $R^{7'}$ is as defined for formula (I) with any reactive groups protected, are also a part of this invention. Preferably, $R^{7'}$ is C_{1-6}alkyl and more preferably C_{3-6}alkyl. Suitably, R^6 is tetrazol-5-yl or 1,3,4-triazol-2-yl, and Pr^2 is H or an arylmethyloxycarbonyl or C_{1-6}alkyloxy group. Benzyloxycarbonyl, wherein the phenyl group is optionally substituted with one to three halogen, methoxy, methylthio or C_{1-4}alkyl groups, is representative of the arylmethyloxycarbonyl group.

The compounds of formula (II), (IV) and (VI), wherein R^2 is H, are derived from substituted 5-amino-4-hydroxy-pentanoic acids, which are prepared, for instance, according to Scheme 3.

Scheme 3



Other methods for preparing protected 5-amino-4-hydroxy-2,5-disubstituted-pentanoate esters and acids, and the corresponding γ-lactones, are well known and are disclosed,

for instance, in Szelke *et al.*, U.S. Patent 4,713,455, Boger *et al.*, U.S. Patent 4,661,473, EP-A 0 352 000, Evans *et al.*, J. Org. Chem., 50, 4615 (1985), Kempf, J. Org. Chem., 51, 3921 (1986), Fray *et al.*, J. Org. Chem., 51, 4828 (1986), Halladay *et al.*, Tett. Lett., 24, 4401 (1983), Wuts *et al.*, J. Org. Chem., 53, 4503 (1988), DeCamp *et al.*, Tett. Lett., 32,1867 (1991), and Szelke *et al.*, WO 84/03044, all of which are incorporated herein by reference. The substituted 5-amino-4-hydroxy pentanoic acids may then be coupled, if necessary, via their amino or carboxyl termini to yield the compounds of formula (II), (IV) and (VI).

The compounds of formula (II), (IV) and (VI), wherein R^2 is OH, are also derived by similar methods common in the art such as those disclosed in U.S. Patent 4,864,017, and Thaisrivongs *et al.*, *J. Med. Chem.*, 30, 976 (1987).

Suitable protecting groups for the amino, hydroxyl, carboxylic acid, mercaptan group, and reagents for deprotecting these functional groups are disclosed in Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Second Edition, John Wiley and Sons, New York, 1991. Deprotection indicates the removal of the protecting group and replacement with an hydrogen atom. In particular, suitably substituted acetyl, benzyl and silyl groups are useful for protecting the hydroxyl group. The acetyl group is commonly removed by reacting the compound with a base, such as an alkali metal hydroxide, in a mixture of an alcohol and water. The silyl group, such as trimethyl silyl, dimethyl-t-butyl silyl, and t-butyl-diphenyl silyl may be removed by a fluoride reagent, such as a tetra-alkyl ammonium fluoride, or by acid hydrolysis. The benzyl group may be removed by catalytic hydrogenation.

Suitable protecting groups for the amino group are those disclosed by Greene *et al.*, as indicated previously. The benzyloxycarbonyl and t-butoxycarbonyl groups are especially useful amino protecting groups.

The present invention includes pharmaceutically acceptable acid addition salts. Acid addition salts of the present compounds are prepared in a standard manner in a

suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+, K^+, Ca^{++} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

The compounds of the present invention selectively bind to retroviral proteases in the same manner as the virally coded natural substrates of the proteases and compete with these substrates for protease. This competition serves to inhibit viral replication by blocking the formation of crucial viral proteins from polyprotein precursors by the protease, and hence, to inhibit disease progression *in vivo*.

When a compound of the present invention is administered to an animal infected or potentially infected with a retrovirus, viral replication is inhibited and hence disease progression is retarded. Inasmuch as the amino acid sequences of the protease binding and peptide bond cleavage sites of various retroviruses appear to be highly conserved, an inhibitor is likely to be broadly active against more than one retrovirus. Also, DNA viruses which are dependant upon virally encoded proteases, such as the hepatitis virus, may also be susceptible to such treatment.

The compounds of formula (I) are used to inhibit retroviral replication, and are useful in treating mammals, particularly human patients, who are infected with susceptible retroviruses and require such treatment. The method of treating a retroviral disease in a mammal, particularly a human, comprises internally administering (*e.g.* orally, parenterally, buccally, trans-dermally, rectally or by insufflation) to said mammal an effective amount of a compound of formula (I), preferably dispersed in a pharmaceutical carrier. Dosage units of the active

ingredient may be selected by procedures routine to one skilled in the art, and are generally in the range of 0.01-50 mg/kg. These dosage units may be administered one to ten times daily for acute or chronic infection. Preferably the compound is administered at a level of 1-10 mg/kg, two to four times daily. No unacceptable toxicological effects are indicated when compounds of this invention are administered in the above noted dosage range.

The present invention also provides a method of treating disease states associated with HIV infection or Acquired Immune Deficiency Syndrome (AIDS), comprising administering an effective amount of a compound of formula (I), preferably dispersed in a pharmaceutical carrier.

Beneficial effects may be realized by co-administering, individually or in combination, other anti-viral agents with the protease inhibiting compounds of the present invention. Examples of anti-viral agents include nucleoside analogues, phosphonoformate, rifabutin, ribaviran, phosphonothioate oligodeoxynucleotides, castanospermine, dextran sulfate, alpha interferon and ampligen. Nucleoside analogues, which include 2',3'-dideoxycytidine(ddC), 2',3'-dideoxyadenine(ddA) and 3'-azido-2',3'-dideoxythymide (AZT), are especially useful. AZT is a preferred agent. Suitably, pharmaceutical compositions comprise an anti-viral agent, a protease inhibiting compound of the present invention, and a pharmaceutically acceptable carrier.

This invention is also a pharmaceutical formulation which comprises a compound of formula (I) and a pharmaceutically acceptable carrier. Pharmaceutical acceptable carriers are well known in the art and are disclosed, for instance, in SPROWL'S AMERICAN PHARMACY, Dittert, L. (ed.), J.B. Lippincott Co., Philadelphia, 1974, and REMINGTON'S PHARMACEUTICAL SCIENCES, Gennaro, A. (ed.), Mack Publishing Co., Easton, Pennsylvania, 1985.

Pharmaceutical compositions of the compounds of the present invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of

a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution, but a lipophilic carrier, such as propylene glycol optionally with an alcohol, may be more appropriate for compounds of this invention. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, soy bean oil, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solubilizing agents, such as dimethylsulfoxide, ethanol or formamide, may also be added. Carriers, such as oils, optionally with solubilizing excipients, are especially suitable. Oils include any natural or synthetic non-ionic water-immiscible liquid, or low melting solid, which is capable of dissolving lipophilic compounds. Natural oils, such as triglycerides are representative. In fact, another aspect of this invention is a pharmaceutical composition comprising a compound of formula (I) and an oil.

Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Solubilizing agents, such as dimethylsulfoxide or formamide, may also be added. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per

dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

The pharmacological activity of the compounds of this invention may be demonstrated by enzyme assays to determine the inhibitory activity of the retroviral protease, by *in vitro* cellular-based assays to determine the ability of the compounds to penetrate cells and inhibit viral replication, and by pharmacokinetic assays to determine oral bioavailability, drug half-life and clearance. Such assays are well known in the art.

ENZYME ACTIVITY

The ability of the compounds of this invention to inhibit the HIV-1 protease enzyme may be demonstrated by using the assay disclosed by Dreyer *et al.*, *Proc. Natl. Acad. Sci., U.S.A.*, 86, 9752 (1989), Grant *et al.*, *Biochemistry*, 30 8441 (1992), and EP-A 352 000. The compound of Example 7(a) showed a Ki of less than 2 µM. The compounds of Examples 3, 7(b) and 7(c) showed a Ki of less than 250 nM. The compounds of Examples 2, 4 and 6 showed a Ki of less than 80 nM. The compounds of Examples 1 and 5 showed a Ki of less than 10 nM.

INFECTIVITY

The ability of the compounds of this invention to gain entry to cells infected with the human immunodeficiency virus, and to inhibit viral replication *in vitro* may be demonstrated using the assay described by Meek *et al.*, *Nature*, 343, 90 (1990), and Petteway *et al.*, *Trends Pharmacol. Sci*, 12, 28 (1991). The compounds of Examples 1, 4 and 5 showed IC50 of less than 2 μM.

CYTOTOXICITY

Cytoitoxicity is assessed by both direct microscopic examination of trypan blue stained cells (T-lymphocytes) and by the treated culture's ability to metabolize the tetrazolium salt XTT (2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide sodium salt), to its formazan dye. The XTT assay allows determination of the 50% toxic concentration of compounds for the cell/virus system used.

The Examples which follow serve to illustrate this invention. The Examples are not intended to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

In the Examples, all temperatures are in degrees Centigrade. Mass spectra were performed using fast atom bombardment (FAB) or electro-spray (ES) ionization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR were recorded at 250 MHz using a Bruker AM 250 spectrometer, unless otherwise indicated. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. Multiplicities for NMR spectra are indicated as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets etc. and br indicates a broad signal. J indicates the NMR coupling constant in Hertz.

Celite® is filter aid composed of acid washed diatomaceous silica manufactured by Mansville Corp., Denver,

Colorado. Florisil® is an activated magnesium silicate chromatographic support and is a registered trademark of Floridon Co., Pittsburgh, Pennsylvania. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Example 1

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

a) (S)-1-(1,2,4-triazol-3-yl)-1-benzyloxycarbonylamino-2-methylpropane

N-Benzyloxycarbonyl-valinamide (2.40 g, 9.6 mmol) and dimethylformamide dimethyl acetal (1.25 g, 10.5 mmol) was suspended in 5 mL of anhydrous DMF and heated to 90°C for 15 min, and allowed to cool to room temperature. 5mL of glacial acetic acid was added and stirred vigorously at room temperature. Anhydrous hydrazine (307 mg, 9.6 mmol) was added. A thick precipitate formed immediately. The reaction mixture was heated at 90°C for 2 h and cooled to room temperature. The reaction mixture was poured into 100 mL of ice-water. After approximately 2 h, the white precipitate was filtered and dried under vacuum overnight to yield the title compound (2.45 g, 93%), which was recrystalized from methanol-water. ^{1}H NMR (CDCl3, 250MHz) 0.90 (dd, 6H, J= 14,6 Hz), 2.25 (m, 1H), 4.82 (t, 1H, J=4 Hz), 5.12 (t, 2H, J=6 Hz), 6.02 (br d, 1H, J=4 Hz), 7.20-7.45 (m, 5H), 8.07 (s, 1H); MS(ES) 275 (M+H)+, 231, 214; 547.2 (2M-H)-, 273 (M-H)-, 165, 122.

b) (S)-1-(1,2,4-triazol-3-yl)-1-amino-2-methylpropane

The compound of Example 1(a) (255 mg, 0.93 mmol) and 10% palladium on carbon (15 mg) was suspended in 25 mL of methanol and stirred for 12 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite® and evaporated to yield the title compound (130 mg, 100%). ^{1}H NMR

($CDCl_3$, 250 MHz) 0.90 (dd, 6H, J=6, 1 Hz), 2.12 (m, 1H), 3.95 (d, 1, J=4 Hz), 5.15 (br s , 2H) 8.05 (s, 1H).

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

(2R,4S,5S)-2-Benzyl-4-(t-butyldimethyl)siloxy-5-(t-butyloxycarbonyl)amino-6-phenylhexanoic acid (1.0 g, 1.89 mmol), BOP reagent (840 mg, 1.90 mmol), the compound of Example 1(b) (265 mg, 1.89 mmol), and diiospropylethylamine (538 mg, 4.17 mmol), were stirred in 10 mL of CH_2Cl_2 for 24 h. The reaction mixture was washed with 10% $NaHCO_3$, separated, dried ($MgSO_4$) and evaporated to yield a colorless oil. The crude product was purified (silica gel, CH_2Cl_2/methanol 2%) to yield the title compound (945 mg, 77%). ^1H NMR ($CDCl_3$, 250MHz), 0.05 (s, 6H), 0.75 (d, 6H, J=3Hz), 0.90 (s, 9H), 1.35 (s, 9H), 1.52-1.80 (m, 2H), 2.28 (m, 1H, J=3 Hz), 2.50-2.90 (m, 5H), 3.72 (m, 1H), 4.00 (m, 1H), 4.65 (t, 1H, J=3 Hz), 4.73 (d, 1H, J=4 Hz), 6.50 (d, 1H, J=3 Hz), 6.90-7.40 (m, 10H), 7.82 (s, 1H).

d) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

The compound of Example 1(c) (945 mg, 1.45 mmol) was dissolved in 10 mL of anhydrous THF. Tetrabutylammonium fluoride 1.0 M solution in THF (8.74 mL, 8.74 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was redissolved in CH_2Cl_2, washed with brine, water, separated, dried ($MgSO_4$) and evaporated to yield a colorless oil. The crude product was purified (silica gel) to yield of the title compound as a white foam (550 mg, 71%). ^1H NMR (CD_3OD, 400 MHz), 0.65 (d, 3H, J=3 Hz), 0.85 (d, 3H, J=3 Hz), 1.30 (s, 9H), 1.55 (t, 1H, J=3Hz), 1.62, (t, 1H, J=3 Hz), 1.97 (m, 1H), 2.50-2.83, (m, 5H), 3.49, (d, 1H, J=4 Hz), 3.62 (t, 1H, J=2 Hz), 4.72 (d, 1H, J=3 Hz), 6.20 (d, 1H, J=4 Hz), 6.90-7.40, (m, 10H), 8.12,

(br s, 1H);. MS(FAB) 558 $(M+Na)+$, 536 $(M+H)+$; 580 $(M+HCO_2)-$, 570 $(M+Cl)-$, 534 $(M-H)-$.

Example 2

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

a) (S)-1-(5-methyl-1,2,4-triazol-3-yl)-1-benzyloxycarbonylamino-2-methylpropane

N,N-dimethylacetamide (57 mg, 0.65 mmol) was added to a solution of trimethyloxonium tetrafluoroborate (100 mg, 0.68 mmol) in methylene chloride (2 mL) and the reaction stirred for 30 min After this time the methylene chloride was removed by distillation *in vacuo* and anhydrous dimethylformamide (3 mL) was added.

Z-valamide (160 mg, 0.65 mmol) was then added and the reaction mixture heated to 90°C for 30 min, cooled to room temperature and treated with glacial acetic acid (2 mL) followed by hydrazine (21 mg, 0.65 mmol). The resultant solution was reheated to 90°C. After 2 hours, the reaction mixture was poured into ice water (25 mL) and extracted with chloroform (3 X 50 mL). The combined extracts were dried (sodium sulfate), filtered, and concentrated to afford a yellow oil.The oil was chromatographed (Silica; 5% methanol/methylene chloride) to afford the 5-methyltriazole as a white solid (23 mg, 13%):

^1H NMR ($CDCl_3$, 250 MHz) δ).85 (d, 3H, J=2 Hz), 0.89 (d, 3H, J=2 Hz), 2.14 (m, 1H), 2.42 (s, 3H), 4.85 (m, 1H), 5.02 (s, 2H), 5.38 (bd, 1H, J=7 Hz), 7.38 (s, 5H); MS(ES/Na^+CHOO^-) m/e 312 $(M+ Na)^+$, 290 $(M+H)^+$.

b) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(5-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

The methyltriazole of Example 2a (23 mg, 0.08 mmol) in methanol (5 mL) was hydrogenated for 1 h at 25°C.(1 atm) in

the presence of 10% palladium on charcoal (1 mg). After this time the mixture was filtered and the solution concentrated *in vacuo* to yield a colourless oil which was dissolved in methylene chloride (5 mL) and coupled to (2R,4S,5S)-2-benzyl-4-(t-butyldimethyl)siloxy-5-(t-butyloxycarbonyl)amino-6-phenylhexanoic acid (31 mg, 0.071 mmol) by the procedure of Example 1(c) to yield the title compound (43 mg, 81%).

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

The compound of Example 2(b) (43 mg, 0.065 mmol) in THF (3 mL) was treated with a solution of tetrabutylammonium fluoride (1M, 250 μL). The solution was stirred for 12 h, then concentrated *in vacuo* Preparative HPLC (4% methanol/methylene chloride) yielded the title compound (5.5 mg, 15%). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.1-7.3 (m, 10H), 5.95 (brd, 1H), 4.96 (m, 1H), 4.63 (brd, 1H), 3.71 (m, 2H), 2.90 (m, 4H), 2.67 (d, 2H, J=7.5 Hz), 2.43 (s, 3H), 2.11 (m, 1H), 1.81 (m, 2H), 1.38 (s, 9H), 1.21 (m, 1H), 0.91 (d, 3H, J=6 Hz), 0.83 (d, 3H, J=6.2 Hz); MS(ES, Na^+CHOO^-) m/e 550 $(M+H)^+$, 548 $(M-H)^-$, 594 $(M+CHOO)^-$.

Example 3

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

a) (S)-1-(5-methyl-1,2,4-triazol-3-yl)-1-benzyloxycarbonylamino-2-methylpropane

N,N-dimethylformamide dimethylacetal (248 mg, 2.0 mmol) was added to a solution of benzyloxycarbonyl-valinamide (520 mg, 2.0 mmol) in anhydrous dimethylformamide (3 mL). The reaction mixture was heated to 90°C for 30 min, cooled to room temperature and treated with glacial acetic acid (2 mL) followed by N-methylhydrazine (97 mg, 3.0 mmol). The resultant solution was reheated to 90°C. After 2 h the

reaction mixture was poured into ice water (25 mL) worked up in a manner analogous to example 2a to afford the title compound as a white solid (102 mg, 20%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ).0.75 (t, 3H, J=6.9 Hz), 0.98 (d, 3H, J=6.7 Hz), 2.14 (m, 1H),3.87 (s, 3H), 4.61 (m, 1H), 5.02 (AB, 2H, J=8.7), 6.06 (bd, 1H, J=7 Hz), 7.26 (s, 5H), 7.76 (s, 1H); MS(ES/Na^+CHOO^-) m/e 312 $(M+ Na)^+$, 290 $(M+H)^+$.

b) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

The compound of Example 3(a) (100 mg, 0.35 mmol) in methanol (5 mL) was hydrogenated for 1.5 h at 25°C.(1 atm) in the presence of 10% palladium on charcoal (6 mg). After this time the mixture was filtered and the solution concentrated *in vacuo* to yield a colourless oil which was dissolved in methylene chloride (5 mL) and coupled to (2R,4S,5S)-2-benzyl-4-(t-butyldimethyl)siloxy-5-(t-butyloxycarbonyl)amino-6-phenylhexanoic acid (166.5 mg, 0.32 mmol) by the procedure of Example 1(c)to yield the title comopound (189 mg, 89%).

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide

The compound of Example 3(b) (189 mg, 0.28 mmol) in THF (3 mL) was treated with a solution of tetrabutylammonium fluoride (1M, 800 µL). The solution was stirred for 12 h, then concentrated *in vacuo*. Preparative HPLC (3% methanol/methylene chloride) yielded the title compound (96 mg, 62%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.73 (d, 3H, J=6), 0.92 (d, 3H, J=6), 1.46 (s), 9H), 1.82 (m, 2H), 2.13 (m, 1H), 2.68 (d, 2H, J=7), 2.85 (m, 4H), 3.72 (m, 2H), 3.88 (s, 3H), 4.84 (t, 1H, J=7), 5.08 (db, 1H, J=7), 6.8-7.4 (m, 10H), 7.78 (s, 1H); MS(ES/Na^+CHOO^-) m/e 550 $(M+H)^+$, 548 $(M-H)^-$, 594 $(M+CHOO)^-$.

Example 4

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(1-phenylpropyn-3-yl)-hexanamide

a) (3R,5S)-((1'S)-(t-butyloxycarbonyl)amino-2'-phenylethyl)-3-(1'-phenylpropyn-3'-yl)tetrahydrofuran-2-one

To a solution of lithium diisopropyl amide (3.61 mL, 2.0 M in THF; 2.2 equiv) at -78°C under Argon was added (5S)-((1'S)-(t-butyloxycarbonyl)amino-2'-phenylethyl)-tetrahydrofuran-2-one (1.0 g, 1.0 equiv.). After 15 min stirring, HMPA (1.14 mL; 2 equiv) was added. After an additional 10 min, phenyl propargyl bromide (1.28 g; 2.0 equiv) was added and the mixture was stirred at -78°C for 2 h. The reaction mixture was diluted with 3N aq HCl and extracted with CH_2Cl_2. The organic extracts were concentrated to an oil. Chromatography (silica gel, 20% ethyl acetate/hexane) provided the title compound as a white solid (0.455 g, 33%). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.18 (10H, m), 4.50 2H, m), 3.93 (1H, q), 2.79 (5H, m), 2.23 (2H, m), 1.24 (9H, s).

b) (2R,4S,5S) 2-(1-phenylpropyn-3-yl)-4-(t-butyldimethyl)siloxy-5-(t-butyloxycarbonyl)amino-6-phenyl hexanoic acid

The titled compound (0.496 g, 84%) was prepared from the compound of Example 4(a) (0.45 g) by the procedure described in Evans, B. E. *et al.* (1985), *J. Org. Chem.* *50*, 4615. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.49-7.10(10H, m), 4.71(1H, d), 3.94(3H, m), 2.69(4H, m), 1.90(2H, m), 1.31(9H, s), 0.89(9H, s), 0.11(6H, d).

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(1-phenylpropyn-3-yl)-hexanamide

The titled compound (0.177 g, 58%) was prepared from (2R,4S,5S)-2-(1-phenylpropyn-3-yl)-4-(t-butyldimethyl)siloxy-

5-(t-butyloxycarbonyl)amino-6-phenylhexanoic acid (0.25 g) and the compound of Example 1(b) by using the coupling procedure of Example 1(c). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.18(11H, m), 4.61(2H, m), 3.84(2H, m), 2.60(5H, m), 1.66(2H, m), 1.52(1H, m), 1.20(9H, s), 0.84(9H, s), 0.77(6H, dd), 0.09(6H, d).

d) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(1-phenylpropyn-3-yl)-hexanamide

Deprotection of the compound 4(c) (0.144 g) with $(n\text{-}Bu)_4NF$ as described in Example 1(d) provided the title compound (0.100 g) in 83% yield. ^{1}H NMR (CD_3OD, 250 MHz) δ 7.72(1H, s), 7.16(10H, m), 6.04(1H, d), 3.61(2H, m), 3.15(1H, m), 2.88-2.36(5H, m), 2.04(1H, m), 1.76(2H, m), 1.28(9H, s), 0.94(1H, m), 0.77(6H, dd); MS: m/z 560.2 $(M+H)^+$, 504.2, 486.2, 460.2, 442.2.

Example 5

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(*trans*-1-phenylpropen-3-yl)-hexanamide

The titled compound was prepared as described in Example 4, starting except substituting 3-phenyl-prop-2-enyl bromide for phenyl propargyl bromide in step 4(a). ^{1}H NMR ($CDCl_3$) 0.71 (d, J = 7 Hz, 3H), 0.84 (d, J = 7 Hz, 3H), 1.36 (s, 9H), 1.71 (m,2H), 2.05 (m,1H), 2.17 (m,1H), 2.34 (m,1H), 2.58 (m,1H), 2.82 (m,1H), 2.98 (m,1H), 3.29 (m,1H), 3.35 (m,1H), 5.93 (m,1HH), 6.26 (d, J = 16 Hz,1H), 7.15 (m,10H), 7.70 (br s,1H); MS(ES) m/z 562 $(M+H^+)$.

Example 6

Preparation of (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(tetrazol-5-yl))methyl-2-phenylmethyl-hexanamide

a) (S)-1-(tetrazol-5-yl)-1-benzyloxycarbonylamino-2-methylpropane

Sodium azide (290 mg, 4.5 mmol) and ammonium chloride (240 mg, 4.5 mmol) were added to a solution of (S)-2-(carbobenzyloxy)amino-3-methylbutyronitrile (940 mg, 4.1 mmol) in anhydrous dimethylformamide (15 mL). The reaction mixture was heated to 125°C for 28 h, cooled to room temperature and treated with 5% hydrochloric acid (5 mL). The dimethylformamide was removed *in vacuo* to afford a resinous mass which was dissolved in water (5 mL). The pH of this solution was adjusted to pH 9 with 5% NaOH and this solution extracted with ether. The pH of the aqueous solution was then adjusted to pH 2 with 5% HCl at which point the tetrazole precipitated. The precipitate was collected by vacuum filtration and washed with ice-water and air-dried to afford the title compound (694 mg, 65%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.89 (d, 3H, J=3 Hz), 1.03 (d, 3H, J=3 Hz), 2.41 (m, 1H), 4.89 (t, 3H, J=6 Hz), 5.10 (q, 2H, J=9), 5.88 (brd, 1H, J=6), 7.33 (s, 5H); MS(ES/Na^+CHOO^-) m/e 298 $(M+ Na)^+$, 276 $(M+H)^+$, 274 $(M-H)^-$.

b) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(tetrazol-5-yl))methyl-2-phenylmethyl-hexanamide

The tetrazole of Example 1a (110 mg, 0.35 mmol) in methanol (7.5 mL) was hydrogenated for 1 h at 25°C.(1 atm) in the presence of 10% palladium on charcoal (12 mg). After this time the mixture was filtered and the solution concentrated *in vacuo* to yield the free amine as a colourless oil (53 mg, 0.42 mmol, 99%) which was dissolved in methylene chloride (5 mL) and coupled to (2R,4S,5S)-2-benzyl-4-(t-butyldimethyl)siloxy-5-(t-butylcarbonyl)amino-6-phenylhexanoic acid (200 mg, 0.38 mmol) using the procedure of Example 1(c). Chromatography (silica gel, 3% methanol/methylene chloride) yielded the title compound (187 mg, 76%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.73 (d, 3H, J=6.5 Hz), 0.84 (d, 3H, J=6.7), 0.92 (s, 9H), 1.32 (s, 9H), 1.74 (m, 1H), 2.4-2.9 (m, 7H), 3.47 (q,

1H, J=7.1 Hz), 3.71 (m, 1H), 3.96 (m, 1H), 4.76 (bd, 1H, J=9 Hz), 4.88 (t, 1H, J= 9), 6.78 (bd, 1H, J=9 Hz), 6.9-7.4 (m, 10H); MS(ES/Na^+CHOO^-) m/e 673 (M+ Na)$^+$, 651 (M+H)$^+$, 649 (M-H)$^-$.

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(tetrazol-5-yl))methyl-2-phenylmethyl-hexanamide

The compound of Example 6(b) (160 mg, 0.25 mmol) in THF (2 mL) was treated with a solution of tetrabutylammonium fluoride (1M in THF, 1.25 mL). The solution was stirred for 12 h, and concentrated *in vacuo*. Preparative HPLC (silica gel, 5% methanol/methylene chloride) yielded the title compound (27 mg, 21%). ^{1}H NMR (CD_3OD, 250 MHz) δ 0.54 (d, 3H, J=5), 0.73 (d, 3H, J=5), 1.28 (s, 9H), 1.57 (m, 2H), 1.95 (m, 1H), 2.3 - 2.7 (m, 6H), 3.22 (S, 1H), 3.38 (m, 1H), 3.52 (m, 1H), 4.71 (m, 1H), 5.28 (db, 1H, J=8), 6.6-7.4 (m, 10H); MS (FAB) m/e 537 (M+H)$^+$, 559 (M+ CHOO)$^-$.

Example 7

Using the procedures analogous to those disclosed above, the following compounds were prepared:

a) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-nitro-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

b) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-amino-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide; and

c) (2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(4,4,4-trifluorobutyl)-hexanamide.

Example 8

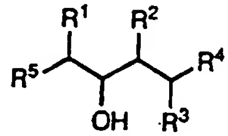
A suitable dosage form for oral administration has been prepared by dissolving the peptide of Example 2 (312.5 mg) in dimethyl sulfoxide (1 mL) and diluting to a concentration of 12.5 mg/mL with soybean oil. The liquid may be encapsulated in a suitable soft gelatin capsule for administration.

Example 9

A suitable dosage form for intravenous administration has been prepared by dissolving the compound of Example 1 (0.02 g) in dimethyl sulfoxide (1 mL) and diluting to 20 mL with a 70% propylene glycol/30% ethanol solution.

What is claimed is:

1. A compound of the formula (I):



(I)

wherein:

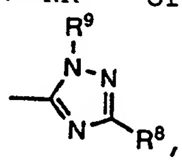
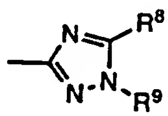
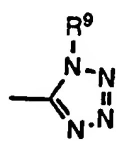
R^1 and R^3 are each independently Q, Q-C_{1-6}alkyl, Q-C_{2-6}alkenyl, Q-C_{2-6}alkynyl or C_{1-6}alkyl substituted by one to five fluorine atoms, each optionally substituted by R^{23};

Q is H, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, Ar or Het

R^2 is H or OH;

R^4 is R^6-NR^{11}- or $CONR^{11}CHR^6R^7$;

R^5 is R^6-NR^{11}- or R^{10}-NR^{11}-;

R^6 is   or  ;

X is NR^{11}, O or S;

R^7 is Q, Q-C_{1-6}alkyl or Q-C_{2-6}alkenyl;

R^8 is H, OH, halo, NO_2, COR^{12}, CF_3, Ar, C_{1-6}alkyl-R^{15}, or $R^{17}(R^{18}R^{19}C)_m$;

R^9 and R^{11} are H or C_{1-4}alkyl;

R^{10} is A-$(B)_n$-;

R^{12} is R^7, OR^7, NR^7R^{11} or an amino acid or amino alcohol;

B is an amino acid;

A is H, Ar, Het, $R^{17}(R^{18}R^{19}C)_m$, Ar-W, Het-W or $R^{17}(R^{18}R^{19}C)_m$-W, or phthaloyl each optionally substituted by one to three groups chosen from R^{15} or C_{1-6}alkyl-R^{15};

W is C=O, OC(=O), $NR^{11}C(=O)$, SC(=O), $NR^{11}C(=S)$, SO_2, $NR^{11}SO_2$ or $P(=O)(OR^{22})$;

R^{15} is H, nitro, C_{1-6}alkoxy, C_{1-6}alkylthio, $O(C=O)R^{16}$, $C=OR^{22}$, CO_2R^{22}, $CON(R^{16})_2$, $N(R^{22})_2$, NHC(=N)NH-A, I, Br, Cl, F, OR^{10}, or OH, provided that when R^{15} is a substituent of the carbon adjacent to W, R^{15} is not halogen or OH when W is OC(=O) or NHCO;

R^{16} is H or C_{1-6}alkyl;

R^{17}, R^{18} and R^{19} are independently: i) H, R^{15} or C_{1-4}alkyl, C_{2-6}alkenyl, phenyl, naphthyl, C_{3-6}cycloalkyl or Het, each optionally substituted by one to three R^{15} or R^{15}-C_{1-6}alkyl groups, or ii) R^{17} is as above and ($R^{18}R^{19}C$) are joined together to form a phenyl, naphthyl, C_{3-6}cycloalkyl or Het ring, or iii) R^{17} is as above and R^{18} and R^{19} together are =O;

R^{22} is H, C_{1-6}alkyl, phenyl or phenyl-C_{1-4}alkyl;

R^{23} is $-X'-(CH_2)_qNR^{24}R^{25}$, $X''[((CH_2)_rO)_s]R^{26}$, $CH_2X''[((CH_2)_rO)_s]R^{26}$, or benzofuryl, indolyl, azacycloalkyl, azabicyclo C_{7-11}cycloalkyl or benzopiperidinyl, optionally substituted with C_{1-4}alkyl;

q is 2-5;

s is 1-6 and r is 1-3 within each repeating unit s;

X' is CH_2, O, S or NH;

X" is CH_2, NR', O, S, SO or SO_2;

R^{24} and R^{25} are i) C_{1-6}alkyl, optionally substituted by OH, C_{1-3}alkoxy, or $N(R')_2$, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, O, S, SO, SO_2, said heterocycle optionally substituted with C_{1-4}alkyl, iii) aromatic heterocycle, optionally substituted with C_{1-4}alkyl or $N(R')_2$;

R' is H or C_{1-4}alkyl;

R^{26} is H, C_{1-4}alkyl, $C(=O)R^{27}$, $C(=O)U[(CH_2)_mO]nR'$, $P(=O)(OM)_2$, CO_2R^{27}, $C(=O)NR^{27}R^{28}$, where M is a mono or divalent metal ion, and U is NR' or O;

R^{27} is C_{1-6}alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C_{1-3}alkoxy, $CONR'_2$, NR'_2, CO_2R', $SO_2NR'_2$, CH_2NR_2, NR'COR', $NR'SO_2R'$, $X''[(CH_2)_rO]_sR'$ or $CH_2X''[(CH_2)_rO]_sR'$;

R^{28} is H, C_{1-6}alkyl or together with R^{27} forms a 5-7 membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

m is 1-4; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 and R^3 are C_{1-6}alkyl, Ar-C_{1-6}alkyl, Ar-C_{2-6}alkenyl, Ar-C_{2-6}alkynyl, C_{1-6}alkyl optionally substituted by one to five fluorine atoms

3. A compound according to claim 1 wherein R^4 is $CONR^{11}CHR^6R^7$.

4. A compound according to claim 2 wherein R^6 is triazole and R^7 is C_{1-6}alkyl

5. A compound according to claim 4 wherein A is C_{1-6}alkylOC(=O), pyridinylmethyloxycarbonyl or arylmethyloxycarbonyl, and R^2, R^9 and R^{11} are H.

6. A compound according to claim 1 which is:

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxy-carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(5-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1-methyl-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(1-phenylpropyn-3-yl)-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(*trans*-1-phenylpropen-3-yl)-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(tetrazol-5-yl))methyl-2-phenylmethyl-hexanamide;

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(5-nitro-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide;

2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(5-amino-1,2,4-triazol-3-yl))methyl-2-phenylmethyl-hexanamide; or

(2R,4S,5S,1'S)-6-phenyl-5-(t-butyloxycarbonyl)amino-4-(t-butyldimethyl)siloxy-N-(1'-isopropyl-1'-(1,2,4-triazol-3-yl))methyl-2-(4,4,4-trifluorobutyl)-hexanamide.

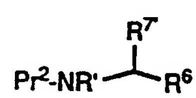
7. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

8. A method of inhibiting a retroviral protease comprising administering an effective amount of a compound according to Claim 1.

9. The use of a compound according to Claim 1 in the manufacture of a medicament for treating infection by a retrovirus.

10. A method of treating disease states associated with HIV infection comprising administering an effective amount of a compound according to Claim 1.

11. A compound of formula (VIII):



(VIII)

wherein,

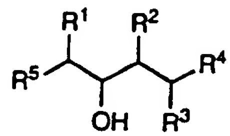
Pr^2 is an amino protecting group;

R' is H or C_{1-4}alkyl;

R^6 is as defined in claim 1; and

$R^{7'}$ is as defined in claim 1 with any reactive groups protected.

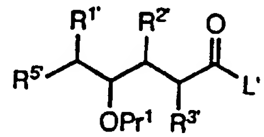
12. A process for preparing a compound of the formula:



(I)

wherein R^4 is CO-NR'CHR^{6}R^7, R^5 is $R^{10}R^{11}N$-, and R^1, R^2, R^3 and R^6 are as defined in formula (I), which comprises,

1) (a) coupling a compound of the formula (II):



(II)

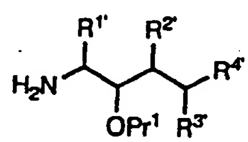
with a compound of formula (III):

HR'N-CHR$^{6'}$R$^{7'}$

(III)

where $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{5'}$, $R^{6'}$ and $R^{7'}$ are as defined for formula (I) with any reactive groups protected, Pr^1 is H or a hydroxyl protecting group, and L' is OH or a leaving group; or

(b) coupling a compound of the formula (IV):



(IV)

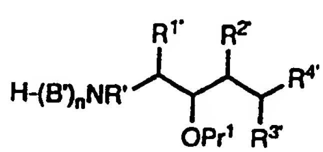
with a compound of the formula (V):

A'-(B')$_n$-L'

(V)

wherein A' and B' are as defined in formula (I) with any reactive groups protected; or

(c) coupling a compound of the formula (VI):



(VI)

with a compound of the formula (VII):

A'-L'

(VII)

and,

2) if appropriate, a coupling agent; and

3) removing any protecting groups and

4) forming a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01785

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 255/02, 257/04; A61K 31/41; C07F 07/02
US CL :548/255; 265.4, 110; 514/63, 359, 381, 383
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/255; 265.4, 110; 514/63, 359, 381, 383

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 3,997,551, (MINAGAWA et al), 14 Dec. 1976. See entire document	1-11
A	US,A, 4,038,406, (Meiser et al) 26 July 1977. See entire document	1-11
A	US,A, 4,505,919 (Cooper et al) 19 March 1985. Seen entire document	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 JULY 1993	29 JUL 1993

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DAVID SPRINGER
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I Claims 1-11 drawn to compounds, composition and method of use
Group II Claim 12 drawn to multiple methods of preparing compounds of Group I,
On claims 1-11 of Group I were searched because claim 12 Group II was found to be unsearchable as indicated above.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: ______________________

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)